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(54) Title: IMPROVED INTRAOCULAR IRRIGATING SOLUTION CONTAINING NON-STEROIDAL ANTIINFLAMMATORY AGENT

(57) Abstract

Pharmaceutical compositions useful in ophthalmic surgery are described. The compositions include one or more non-steroidal antiinflammatory drugs, and are useful for preventing or treating ophthalmic inflammation and other conditions associated with ophthalmic surgery. Methods of using the compositions in connection with ophthalmic surgical procedures are also described.

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IMPROVED INTRAOCULAR IRRIGATING SOLUTION CONTAINING NON-STEROIDAL ANTIINFLAMMATORY AGENT

Background of Invention:

1. Field of the Invention

The present invention relates to the field of ophthalmology. More particularly, the invention relates to an improved solution for maintaining the integrity, stability, and function of ocular tissues during invasive surgical procedures.

2. Discussion of Related Art

The growth of new surgical techniques and associated products over the past decade has been quite remarkable. For example, cataract surgery, which is a very delicate operation involving replacement of the natural crystallin lens of the human eye with an artificial lens, was previously considered to be a major surgical procedure requiring hospitalization of the patient and a significant recovery period, but today this procedure is routinely performed on an out-patient basis and enables vision to be restored almost immediately. Similar advancements have been achieved in other areas of ophthalmic surgery. These remarkable advancements are attributable to various factors, including improved equipment for performing the surgeries, improved surgical techniques developed by innovative surgeons, and improved pharmaceutical products which facilitate successful surgery by minimizing the risks of damaging sensitive, irreplaceable ocular tissue during surgery. The present invention is directed to a further improvement in one such pharmaceutical product, a solution for irrigating ocular tissue during intraocular surgery. Such solutions are discussed in United States Patent No. 4,550,022; the entire contents of that patent are hereby incorporated in the present specification by reference.

The importance of such solutions to ophthalmic medicine is explained in the '022 patent. The relevant portions of that explanation are repeated below.

Any scission into the human body is detrimental to the human body and invariably results in cell loss. The need to keep cell loss to a minimum is particularly crucial during any surgical procedure performed on delicate and irreplaceable tissues, such as the tissues of the eye, nerves, etc.

The cornea of the eye is comprised of five layers: epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium. The endothelium layer is particularly vulnerable to trauma as the endothelial cells are infrequently, if ever, replaced as a normal process in the adult life. The endothelium is principally responsible for the maintenance of the proper state of hydration of the stromal layer. The stromal layer has a tendency to imbibe fluid, a tendency which is counter-balanced by outward fluid transport via the endothelium. If the proper fluid balance is not maintained in the stromal layer, the cornea thickens and the characteristic transparency of the cornea is lost. Accordingly, cell loss or damage in the endothelial layer will result in decreased vision. Failure of the endothelium to perform its fluid transport function for short periods of time will result in corneal thickening and visual clouding. Because of the importance of, and the vulnerability of, the endothelial layer, it is necessary during eye surgery, such as cataract and retinal surgery or corneal transplants, to make provisions for the protection of the endothelial cells.

A significant factor causing cell loss during tissue scission is the traumatic change in environment experienced by the internal cells. Exposure to the atmosphere presents a far different environment for the cells than is provided by the natural fluids in which they are bathed. To simulate the natural cellular environment and thereby prevent cell damage, exposed tissue during surgery is frequently irrigated in solutions which attempt to approximate natural body fluids. The value of bathing eye tissue during surgery to prevent cell damage has long been recognized. For internal ocular tissues, such as the endothelium, the aqueous humor is the natural bathing fluid and, hence, an ophthalmic irrigating solution intended to protect the endothelium should as closely as possible resemble the aqueous humor.

Of primary concern in a tissue irrigating solution is that the osmolality of the solution be generally isotonic with cellular fluids so as to maintain equal osmotic pressure within and without the cell membranes. To this end, one of the early ophthalmic irrigating solutions was isotonic (0.9%) saline. However, as has long been recognized, isotonic saline is quite inadequate as an ophthalmic irrigating solution and has been shown to result in endothelial cell swelling, cell damage, and consequent corneal clouding.

Because of the inadequacy of isotonic saline, various alternative electrolyte solutions have been proposed as ophthalmic irrigating solutions in attempts to provide solutions which more closely resemble the aqueous humor and prevent cell damage and corneal clouding. Standard electrolyte solutions primarily intended for injection solutions, such as Ringer's solution and lactated Ringer's solution, have been used as ophthalmic irrigating solutions because of their wide availability as sterile solutions.

A solution intended for ophthalmic irrigation known as "balanced salt solution" has also been developed. Balanced salt solution contains the essential ions, calcium, sodium, potassium, magnesium and chloride in generally optimal concentrations for ocular tissue, and has an acetate-citrate buffer system which is compatible with divalent calcium and magnesium ions.

The various electrolyte solutions used for ophthalmic irrigation have been improvements over normal saline by providing necessary ions in addition to Na^+ and Cl^- as provided by isotonic saline. Mg^{++} is an important cofactor for adenosine triphosphatase, an enzyme which plays an important role in mediating the fluid transport pump in the eye. Ca^{++} is necessary to maintain the endothelial junction. K^+ is an important factor in many biochemical processes, and the fluid transport pump of the endothelium requires a proper Na^+/K^+ ratio.

During eye surgery and particularly during surgery which requires extended periods of time, proper electrolytic balance alone is insufficient to retain normal corneal thickness. To maintain proper corneal thickness and prevent cell damage, an irrigating solution in addition to electrolytic balance must provide metabolic support and must particularly provide factors needed for the enzyme-mediated Na^+/K^+ pump system through which excess fluid is removed from the stroma.

To incorporate factors necessary for sustained metabolism by endothelial cells, glutathione-bicarbonate-Ringers solution ("GBR") was developed in which $NaHCO_3$, glutathione, dextrose and adenosine (an optional ingredient) are added to Ringer's solution. Bicarbonate, dextrose and glutathione have been shown to be important factors in maintaining structural integrity of endothelial cells. Bicarbonate is included because the aqueous humor has a bicarbonate buffer system; dextrose (d-glucose) provides a substrate for various metabolic pathways; and glutathione has been shown to aid the metabolic pump mechanism by maintaining proper Na^+/K^+ adenosine-triphosphatase. GBR has been shown effective in maintaining corneal thickness and endothelial cell integrity for up to three hours.

While the effectiveness of a GBR ocular irrigating solution has been known for many years, prior to the early 1980's its use in surgery was quite limited due to stability and sterility problems. It is to be appreciated that sterility of an ophthalmic irrigating solution is absolutely essential. To insure sterility, it is desirable that an irrigating solution be prepackaged so that the quality and sterility may be closely monitored and tested as contrasted with an extemporaneously mixed solution as might be prepared in a hospital pharmacy. The solution will perfuse the eye in essentially a closed system where even a small number of organisms, such as *pseudomonas aeruginosa*, can produce an overwhelming endophthalmitis.

GBR may not be prepackaged due to the long term incompatibility and/or instability of its various moieties. Of the moieties added to Ringer's solution to formulate GBR, bicarbonate is perhaps the most important. The bicarbonate as well as the phosphate in a bicarbonate-phosphate buffer system may form insoluble precipitates with Mg^{++} and Ca^{++}. While at the ionic concentrations useful in ophthalmic irrigation, precipitation is not a problem in freshly prepared solution, long-term storage is proscribed. As insoluble crystals introduced into the eye will cloud vision, the importance of keeping a tissue irrigating solution free of insoluble precipitates may be readily appreciated.

Complicating the maintenance of GBR's stability is the fact that the pH of GBR will gradually increase due to the inadequacy of the bicarbonate-phosphate buffer. To provide proper pH, i.e., about 7.4, the pH of the original GBR solutions prepared in the

hospital pharmacy had to be monitored and adjusted with CO_2 immediately prior to use and even during use. The chances for contamination during pH adjustment was great.

A further factor which proscribes long-term storage of GBR is the unavailability of a proper pH at which all of the moieties are stable. Several moieties of GBR are unstable at the physiological pH of about 7.4. Below a pH of about 8, bicarbonate generally decomposes to CO_2, resulting both in a loss of bicarbonate concentration and increased pH. On the other hand, glucose stability requires a pH of less than about 6. Glutathione, while biologically effective either in reduced or oxidized form, is preferred in the oxidized form because the reduced form quickly oxidizes in aqueous solutions, preventing proper labeling of the irrigating solution. Oxidized glutathione (glutathione disulfide) is unstable over extended periods of time at a pH of above about 5. The concentration of glutathione may also decrease to an unacceptable concentration when stored over long periods of time in admixture with all other components. Because of the demonstrated efficacy of GBR as an ocular irrigating solution, it was highly desirable to provide a formulation which contains the essential factors found in GBR and which could be stored in a sterilized form for use in eye surgery. The invention described in U.S. Patent No. 4,550,022 provided such a product. An embodiment of the two-part irrigating solution described in U.S. Patent No, 4,550,022 known as "BSS Plus® Intraocular Irrigating Solution" was introduced by Alcon Laboratories, Inc., Fort Worth, Texas, in the early 1980s.

Ophthalmic irrigating solutions such as BSS Plus® Intraocular Irrigating Solution serve to maintain the physical integrity and function of ophthalmic tissues. The chemical composition of such solutions mimics that of the fluid naturally present within the eye (i.e., "aqueous humor"). Although such solutions are well-suited to maintain the normal function of ophthalmic tissues, these solutions are not directly useful in treating or preventing abnormalities such as inflammation. Since inflammation of ophthalmic tissues is a problem frequently associated with ophthalmic surgical procedures, there has been a need for an improved ocular irrigating solution which not only maintains the physical integrity and function of ophthalmic tissues, but also prevents or alleviates inflammation of those tissues. The present invention is directed to satisfying this need.

Both steroidal and non-steroidal agents have been utilized to treat ophthalmic inflammation. The use of non-steroidal antiinflammatory agents is believed to have certain advantages relative to the use of steroids. Among other things, the non-steroidal agents are relatively soluble in water, while steroids having potent antiinflammatory activity (e.g., dexamethasone) are generally not soluble in water. Moreover, steroids have a propensity to elevate intraocular pressure in some patients. Since intraocular irrigating solutions are generally aqueous, the solubility of an antiinflammatory drug in water is an important consideration.

The use of non-steroidal antiinflammatory agents in conjunction with an intraocular irrigating solution is described in a series of articles by Shimada, et al. See, e.g., Shimada, et al., "Effects of Flurbiprofen on Extracapsular Cataract Extraction", Atarashii Ganka (Journal of the Eye), volume 4, number 5, pages 719-722 (1987). The experiments conducted by Shimada, et al., focused on the ability of flurbiprofen to maintain dilation of the pupil during intraocular surgical procedures. A balanced salt solution was used as the vehicle for the flurbiprofen. Similar experiments involving the use of flurbiprofen and indomethacin in buffered saline solutions are described in Gimbel, "The Effect of Treatment with Topical Nonsteroidal Anti-inflammatory Drugs with and without Intraoperative Epinephrine on the Maintenance of Mydriasis during Cataract Surgery", Ophthalmology, volume 96, number 5, pages 585-588 (1989). The use of indomethacin to reduce swelling and other trauma associated with ophthalmic surgery is described by Alvarez, et al., "Role of the intraocular irrigating solutions in the pathogenesis of the postvitrectomy retinal edema", Current Eye Research, volume 6, number 12, pages 1369-1379 (1987). The use of non-steroidal anti-inflammatory agents to treat corneal endothelial tissues is described in U.S. Patent No. 5,051,443 issued to Neufeld, et al., on September 24, 1991. None of the above-cited publications discloses or suggests the combined use of a nonsteroidal antiinflammatory drug and an ophthalmic irrigating solution of the type described and claimed herein.

Summary of the Invention:

The present invention is directed to the provision of an improved irrigating solution which is generally useful in the prevention or treatment of ophthalmic inflammation, and

is particularly useful in preventing or treating inflammation associated with ophthalmic surgery. More specifically, the invention is directed to irrigating solutions comprising: one or more nonsteroidal antiinflammatory agents, a free radical scavenger to protect corneal endothelial cells, electrolytes to maintain the stability of ophthalmic tissues, an energy source to satisfy the metabolic requirements of corneal endothelial cells and other ophthalmic tissues during surgical procedures, bicarbonate to maintain the fluid pump system of corneal endothelial cells and other ophthalmic tissues, and a buffer.

The invention has a number of advantages relative to prior compositions and methods for treating ophthalmic inflammation. A principal advantage is that the irrigating solutions of the invention perform multiple functions. The solutions prevent cell necrosis and maintain normal cellular functions during ocular surgical procedures, as discussed above, but also modulate intraocular pressure, prevent surgically induced miosis, and suppress post-surgical inflammation and allergic reactions. The solutions are also useful for treating inflammation of ocular tissue associated with ocular surgery or other conditions, such as iritis and conjunctivitis, and preventing cystoid macular edema.

The extemporaneous addition of antiinflammatory agents at the time of surgery presents several significant risks, such as the risk of an improper concentration of the antiinflammatory agent. The present invention eliminates these risk by providing an ophthalmic pharmaceutical composition containing one or more nonsteroidal antiinflammatory agents which is specifically formulated and adapted for use as an intraocular irrigant. Specific advantages of the compositions of the present invention therefore include: (i) delivery of a controlled dose of one or more antiinflammatory agent to the patient; (ii) assurance that the composition is sterile at the time of use, and (iii) adaptation of the pH, osmolality and buffering capacity of the composition so that it is ideally suited for intraocular use.

Description of Preferred Embodiments:

The non-steroidal antiinflammatory drugs ("NSAIDs") used in the present invention may be generally categorized as cyclooxygenase and lipoxygenase antagonists. NSAIDs suppress inflammatory responses by disrupting the synthesis of prostaglandins. More specifically, this class of compounds inhibit cyclooxygenase, and cyclooxygenase converts

arachidonic acids to prostaglandins. ~~NSAIDs~~ have generally diverse chemical structures, but all lack a steroid nucleus. This class of compounds includes various subclasses, based on chemical structure: salicylates, such as aspirin and salicylic acid; fenamic acids, such as flufenamic acid, niflumic acid and mefenamic acid; ~~indoles~~, such as indomethacin, sulindac and tolmetin; phenylalkanoic acids, such as suprofen, ketorolac, flurbiprofen and ibuprofen; phenylacetic acids, such as diclofenac; and enolic acids (also referred to as pyrazolones), such as oxyphenbutazone and phenylbutazone. Further examples of NSAIDs are listed below.

Nimesulide	Amfenac	Indoprofen
Bromfenac	Fenoprofen	Fenclozic acid
Acecloferac	Carprofen	Orpanixin
Flosulide	Flurofenoc	Fenbufen
Mefezoloc	Fenclorac	Benoxaprofen
Lomoxicam	Felbinac	Naproxen
Ketoprofen	Pirprofen	Isofezolac
Trapsufenic acid	Clidanac	Etodolic acid
Proquazine	Loxoprofen	Enfenamic acid
Lornoxicam	BW 7556	

For further background concerning NSAIDs, see J. P. Famaey, et al., Therapeutic Applications of NSAIDs, published by Marcel Dekker, Inc., New York, New York, USA (1992). For a specific discussion of the use of NSAIDs in the field of ophthalmology, see Chapter 16 of that text and the following article: Allan J. Flach, "Cyclo-oxygenase Inhibitors in Ophthalmology", Survey of Ophthalmology, volume 36, number 4, pages 259-283 (1992). The entire contents of both of the above-cited publications are hereby incorporated in the present specification by reference.

The preferred subclasses of NSAIDS for purposes of the present invention are phenylalkanoic acids and phenylacetic acids. The most preferred NSAIDS are bromfenac, suprofen and diclofenac.

The irrigating solutions of the present invention will typically contain one or more NSAIDs in an amount of from about 1 to about 200 millimoles/liter ("mM/l").

The irrigating solutions of the present invention also include an amount of a free radical scavenger effective to protect the corneal endothelial cells and maintain normal function of those cells. The preferred free radical scavengers include ascorbate, glutathione and cysteine, as well as esters, and analogues and other equivalents of these compounds. The most preferred free radical scavenger is glutathione. The solutions will contain one or more free radical scavengers in a concentration of from about 0.01 to about 3 mM/l.

The solutions further comprise: electrolytes in an amount effective to maintain tissue stability; an energy source, such as dextrose, in an amount effective to satisfy the metabolic requirements of corneal endothelial cells and other ophthalmic tissues during the surgical procedure; an amount of bicarbonate effective to maintain the fluid pump system of corneal endothethial cells and other ophthalmic tissues; and a buffer in an amount sufficient to maintain the pH of the composition in the range of 6.8 to 8.0.

The present invention may be embodied in various types of ophthalmic irrigating formulations, but will generally be provided in the form of an aqueous solution. As will be appreciated by those skilled in the art, some of the components of the formulations may need to be segregated prior to the time of use, due to considerations involving the chemical stability of certain components, the potential for adverse chemical interactions between certain components, and the methods of sterilization suitable for certain components, as discussed above under the heading "Background of the Invention".

The most preferred embodiment of the present invention is a two-part product similar to BSS Plus® Intraocular Irrigating Solution. The compositions of the two parts are such that each is individually stable and may be separately stored for long periods.

When mixed together the two parts form a tissue irrigating solution that may be used for surgery during the next 24 hours. The mixed solution is useful for ocular surgery as it contains the necessary factors to maintain endothelial cell integrity and corneal thickness during ocular surgery. The combined irrigating solution contains the necessary ions for tissue stability, Ca^{++}, Mg^{++}, Na^{+}, K^{+} and Cl^{-} in a bicarbonate-phosphate buffer as well as reduced glutathione and dextrose. The electrolytes are provided in proportions conducive to maintaining the physical integrity and metabolism of corneal endothelial cells and other ocular tissues. For this purpose, the irrigating solution will typically contain from about 50 to about 500 millimoles per liter ("mM/l") Na^{+}, from about 1 to about 10 mM/l K^{+}, from about 0.1 to about 5 mM/l Ca^{++}, from about 0.1 to about 10 mM/l Mg^{++} and from about 50 to about 500 mM/l Cl^{-}. To maintain the osmotic stability of the cells, the osmolality is between about 260 and about 330 mOsm and preferably about 290-310 mOsm. So as to closely match the physiological pH of 7.4, the pH of the final irrigating solution is between about 6.8 and about 8.0 and preferably about 7.2-7.8. To maintain the fluid pump system, the bicarbonate concentration in the combined irrigating solution is between about 10 and about 50 mM/l. To stabilize the pH, an additional buffering agent is provided. Preferably the buffering agent is phosphate which is provided in sufficient quantity so that final phosphate concentration of the irrigating solution is between about 0.1 and about 5 mM/l. The final irrigating solution contains between about 1 and about 25 mM/l dextrose and between 0.01 and about 3 mM/l of glutathione.

The neutral solution provides the phosphate and bicarbonate buffering moieties, preferably in the form of dibasic sodium phosphate and sodium bicarbonate. The pH of the solution is adjusted to about the physiological pH, of 7.4, preferably to between about

7.2 and about 7.8. As hereinbefore mentioned, the pH of a bicarbonate-containing solution is preferably above about 8.0 to prevent decomposition of the bicarbonate. It has been found, however, that the bicarbonate may be stabilized if it is added to a solution with a pH of above about 8 and thereafter adjusted to a pH between 7 and 8. Accordingly, when the neutral solution is prepared, Na_2HPO_4 is added prior to the addition of $NaHCO_3$, so that $NaHCO_3$ is dissolved in a solution with a pH of between about 8 and 9. The solution is thereafter adjusted with dilute acid, such as H_2SO_4, H_3PO_4 or HCl, to the desired final pH of the neutral solution. Alternatively, carbon dioxide may be added to adjust the pH.

Potassium and additional sodium are provided in the basic solution in the form of sodium and potassium salts, such as sodium or potassium chlorides, sulfates, acetates, citrates, lactates, and gluconates. The sodium and potassium are compatible with all of the moieties present in the finished tissue irrigating solution, and sodium chloride and potassium chloride may be added to either solution or divided between the solutions. However, in view of the fact that the neutral solution provides the buffer system, the pH of the final irrigation solution may be added to adjust the pH.

The acidic solution provides the Ca^{++} in the form of calcium chloride, the Mg^{++} in the form of magnesium chloride, the glutathione and the dextrose. The pH is adjusted to about 5 or less to provide long-term stability to the dextrose and glutathione.

Because of the requirement that the acidic solution have a low pH, it is preferable that the volume of the neutral solution greatly exceed the volume of the acidic solution and that the acidic solution contain no buffering agents. The acidic solution may be adjusted below a pH of about 5 with a relatively small amount of HCl. Because the

acidic solution is unbuffered, its pH is a reflection of the acid concentration and less acid is needed to adjust the pH of a small volume. The large volume of buffered neutral solution may be adjusted very close to the final pH of the irrigating solution and will be relatively unaffected by the addition of the small volume of the acidic solution. Preferably, the ratio of the neutral solution volume to the acidic solution volume is about 10 to 1 to about 40 to 1.

The neutral solution and the acidic solution are sterilized and separately bottled or contained under sterile conditions by standard techniques, such as autoclaving, or use of sterilizing filters, but preferably by heat sterilization. Typically, the neutral solution, which preferably contains only inorganic moieties, is autoclaved, whereas the acidic solution, which preferably contains the organic components, is microfiltered. To avoid the need for measuring volumes in the hospital which may introduce possible error and/or contamination, it is highly preferred that particular volumes of the neutral and acidic solutions be bottled so that adding the entire content of a container of the acidic solution to the entire content of a container of the neutral solution results in the correctly formulated tissue irrigating solution. The solutions may be mixed up to 24 hours before a surgical procedure without the occurrence of significant pH change and without the formation of detectable precipitates and without degradation.

Precautions to maintain sterility of the solutions and to insure correct mixing of the acidic and neutral solutions cannot be overdone. While the manufacturer may take all due precautions to maintain quality control, carelessness by a technician may render all such precautions for naught. Any opening of a container, no matter how carefully performed, increases the likelihood of contamination in the contents. As one method of substantially

eliminating the possibility of improper mixing and to reduce the likelihood of contamination, the solutions may be shipped in a container having a first chamber for the neutral solution, an isolated second chamber for the acidic solution and means to communicate the chambers without opening the container. Various types of containers for the shipment of multi-part medical solutions may be utilized. As one example, a container may have a lower chamber containing a measured volume of the neutral solution separated by a membrane from an upper chamber containing a measured volume of the acidic solution or a lyophilized powder formed from that solution. The container cap may include a plunger means which, when depressed, causes a sharp point of blade depending therefrom to break the membrane. The container is thereafter agitated, as by shaking, to complete the sterile mixing in proper volume of the acidic and neutral solutions.

The proper mixing of the acidic and neutral solutions may also be carried out by aseptically removing the acidic solution from its package with a sterile syringe and needle and aseptically adding the acidic solution to the contents of the neutral solution package through the rubber stopper. Alternately, a sterile double-ended needle can be used to transfer the acidic solution to the neutral solution by aseptically inserting one end of the needle into the vial containing the acidic solution and then aseptically inserting the other end of the needle into the neutral solution package, whereby the vacuum that is maintained therein transfers the acidic solution to the neutral solution and is mixed. A two compartment syringe can also be utilized, with the lyophilized powder of the acidic solution in one compartment, and a diluent for the powder in the second compartment. The compartments are separated by a movable stopper or membrane which can be displaced by depressing the plunger of the syringe, thereby allowing the diluent to be

combined with the powder. Once the powder is dissolved, the resulting solution is then added to the bottle containing the neutral buffered solution by inserting a cannula attached to the front of the syringe through a stopper in the top of the bottle.

The two-part solution of the present invention also provides an advantage as to safety if a technician should fail to properly mix the two solutions. The larger volume neutral solution is physiologic so that there is less chance of toxicity if the basic solution were used with the acidic solution being mixed therewith.

The present invention may be embodied in various types of formulations. Representative formulations are described in the following examples.

EXAMPLE 1

The following two-part formulation is similar to the BSS Plus® Intraocular Irrigating Solution available from Alcon Laboratories, Inc., Fort Worth, Texas, USA. That product, which is described in United States Patent No. 4,550,022 (Garabedian, et al.), consists of two solutions referred to as "Part I" and "Part II", respectively. The following description illustrates how that product or similar products could be modified to incorporate the present invention.

Part I (neutral solution) is made by dissolving sodium chloride, potassium chloride, and anhydrous dibasic sodium phosphate in water for injection at about 20° C. Then sodium bicarbonate is added and dissolved. Additional water for injection is added to make the desired volume and 1N HCl is added to adjust the pH to about 7.4. The solution is then passed through a 0.45 micron Millipore filter and placed in a bottle. The filled bottle is then stoppered, vacuumed and sealed. The sealed bottle is sterilized by autoclaving at 121° C for about 23 minutes.

Part II (acidic solution) is made by dissolving calcium chloride dihydrate, magnesium chloride hexahydrate, dextrose, and glutathione in water for injection. The solution is then sterile filtered through a 0.22 micron membrane filter and aseptically filled into a presterilized bottle and sealed with a presterilized rubber stopper.

For many free radicals that are sensitive to oxygen, the container is flushed with nitrogen gas. Also, a nitrogen blanket is maintained over the solution to displace air and protect the solution from oxidation. Immediately after flushing the filled container with nitrogen gas, it is sealed by means of a presterilized rubber stopper.

One or more NSAIDS may be added to either the neutral solution or the acidic solution, depending on the PKA of the NSAIDs selected.

When Parts I and II are combined, the composition of the resulting formulation is as follows:

Ingredients	Concentration (mM/l)
Reduced Glutathione	0.01-3.0
NSAID	1-200
Bicarbonate	1-50
Calcium	0.1-5
Magnesium	0.1-10
Potassium	1-10
Sodium	50-500
Phosphate	0.1-5
Glucose	1-25
Chloride	50-500
Sodium Hydroxide and/or	Adjust pH
Hydrochloric Acid	Adjust pH
Water for Injection	q.s.

EXAMPLE 2

The following formulation is a more specific example of the Part I solution described in Example 1 above:

Ingredients	Concentration Grams/Part I (480ml)	Concentration mg/ml
Suprofen	0.4800	1.00
Sodium Chloride, USP	3.5712	7.440
Potassium Chloride, USP	.1896	.395
Dibasic Sodium Phosphate	.2078	.433
Sodium Bicarbonate	.1261	.263*
Purge with CO_2 to Adjust pH		
Water for Injection	q.s. 480 ml	

* Includes 20% excess

The invention may also be embodied in products formulated or configured differently from the two-part product described above. For example, one or more components of the formulation, such as the above-described acidic solution containing glutathione, can be lyophilized (i.e., freeze-dried) following preparation and then reconstituted as a solution prior to use. A formulation of this type is described in United States Patent No. 4,975,419.

What is Claimed is:

1. A pharmaceutical composition for irrigating ophthalmic tissue during an intraocular surgical procedure comprising:

an antiinflammatory effective amount of a nonsteroidal antiinflammatory drug;

an amount of a free radical scavenger effective to maintain normal function of corneal endothelial cells;

electrolytes in an amount effective to maintain tissue stability;

an energy source in an amount effective to satisfy the metabolic requirements of corneal endothelial cells and other ophthalmic tissues during the surgical procedure;

an amount of bicarbonate effective to maintain the fluid pump system of corneal endothethial cells and other ophthalmic tissues; and

a buffer in an amount sufficient to maintain the pH of the composition in the range of 6.8 to 8.0.

2. A composition according to Claim 1, wherein the nonsteroidal antiinflammatory drug comprises a phenylalkanoic acid.

3. A composition according to Claim 1, wherein the nonsteroidal antiinflammatory drug comprises a phenylacetic acid.

4. A composition according to Claim 1, wherein the nonsteroidal antiinflammatory drug is selected from the group consisting of suprofen, bromfenac, diclofenac, ketorolac, flurbiprofen and ibuprofen.

5. A composition according to Claim 1, wherein the composition comprises a first part and a second part, said first part comprising a neutral solution containing the bicarbonate and the buffer, and said second part comprising an acidic solution containing the free radical scavenger, the energy source and the divalent electrolytes, and wherein the nonsteroidal antiinflammatory drug and monovalent electrolytes are contained in either said first part or said second part.

6. A composition according to Claim 5, wherein the free radical scavenger is selected from the group consisting of ascorbate, glutathione and cysteine.

7. A composition according to Claim 5, wherein the free radical scavenger comprises glutathione.

8. A composition according to Claim 5, wherein the composition comprises:

0.1 to 5 mM/l of the free radical scavenger;

1 to 25 mM/l of dextrose;

1 to 200 mM/l of the nonsteroidal antiinflammatory drug;

50 to 500 mM/l Na^+;

1 to 10 mM/l K^+;

0.1 to 5 mM/l Ca^{++};

50 to 500 mM/l Cl^-;

10 to 50 mM/l bicarbonate; and

0.1 to 5 mM/l phosphate.

9. A composition according to Claim 8, wherein the nonsteroidal antiinflammatory drug comprises a phenylalkanoic acid.

10. A composition according to Claim 8, wherein the nonsteroidal antiinflammatory drug comprises a phenylacetic acid.

11. A composition according to Claim 8, wherein the nonsteroidal antiinflammatory drug is selected from the group consisting of suprofen, bromfenac, diclofenac, ketorolac, flurbiprofen and ibuprofen.

12. A composition according to Claim 8, wherein the free radical scavenger is selected from the group consisting of ascorbate, glutathione and cysteine.

13. An improved method of irrigating ophthalmic tissue during intraocular surgical procedures which comprises applying to the affected ocular tissue a composition comprising:

an antiinflammatory effective amount of a nonsteroidal antiinflammatory drug;

an amount of a free radical scavenger effective to maintain normal function of corneal endothelial cells;

electrolytes in an amount effective to maintain tissue stability;

an energy source in an amount effective to satisfy the metabolic requirements of corneal endothelial cells and other ophthalmic tissues during the surgical procedure;

an amount of bicarbonate effective to maintain the fluid pump system of corneal endothethial cells and other ophthalmic tissues; and

a buffer in an amount sufficient to maintain the pH of the composition in the range of 6.8 to 8.0.

14. A method according to Claim 13, wherein the nonsteroidal antiinflammatory drug comprises a phenylalkanoic acid.

15. A method according to Claim 13, wherein the nonsteroidal antiinflammatory drug comprises a phenylacetic acid.

16. A method according to Claim 13, wherein the nonsteroidal antiinflammatory drug is selected from the group consisting of suprofen, bromfenac, diclofenac, ketorolac, flurbiprofen and ibuprofen.

17. A method according to Claim 13, wherein the composition comprises a first part and a second part, said first part comprising a neutral solution containing the bicarbonate and the buffer, and said second part comprising an acidic solution containing the free radical scavenger, the energy source and the divalent electrolytes, and wherein the nonsteroidal antiinflammatory drug and monovalent electrolytes are contained in either said first part or said second part.

18. A method according to Claim 17, wherein the free radical scavenger is selected from the group consisting of ascorbate, glutathione and cysteine.

19. A method according to Claim 17, wherein the free radical scavenger comprises glutathione.

20. A method according to Claim 17, wherein the composition comprises:

0.1 to 5 mM/l of the free radical scavenger;

1 to 25 mM/l of dextrose;

1 to 200 mM/l of the nonsteroidal antiinflammatory drug;

50 to 500 mM/l Na^+;

1 to 10 mM/l K^+;

0.1 to 5 mM/l Ca^{++};

50 to 500 mM/l Cl^-;

10 to 50 mM/l bicarbonate; and

0.1 to 5 mM/l phosphate.

21. A method according to Claim 20, wherein the nonsteroidal antiinflammatory drug comprises a phenylalkanoic acid.

22. A method according to Claim 20, wherein the nonsteroidal antiinflammatory drug comprises a phenylacetic acid.

23. A method according to Claim 20, wherein the nonsteroidal antiinflammatory drug is selected from the group consisting of suprofen, bromfenac, diclofenac, ketorolac, flurbiprofen and ibuprofen.

24. A method according to Claim 20, wherein the free radical scavenger is selected from the group consisting of ascorbate, glutathione and cysteine.